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DK

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/862,444	05/23/97	SHYJAN A	07334/004002

HM22/1122

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EXAMINER	
BURKE, J	

ART UNIT	PAPER NUMBER
1642	17

DATE MAILED: 11/22/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

Office Action Summary

Application No.	Applicant(s)
08/862,442	Shyjan et al
Examiner	**Group Art Unit**
Julie E. Burke, (Reeves), Ph.D.	1642

☒ Responsive to communication(s) filed on *8/26/99 and Declaration filed 9/1/99*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *29, 31-43, and 45-68* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *29, 31-43, and 45-68* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendment, filed May 21, 1999 (Paper No. 13), is acknowledged.

Claims 29, 37-43, and 45-56 have been amended.

Claim 57-68 has been added.

Claims 29, 31-43, and 45-68 are pending.

2. The text of those sections of Title 35, U.S.C. Code not included in this Office Action can be found in a prior Office Action.

Previous Rejections

Priority

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the parent application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for some claims of this application.

This application is a Divisional application of Application No. 08/623,679 filed April 16, 1996, which is a CIP of Application No. 08/412,431 (US Pat No: 5,412,431) filed March 29, 1995, and names the same inventor as the prior applications. The invention is drawn to a series of polypeptides encoded by polynucleotide sequences. Claims drawn to the polynucleotide sequence defined by SEQ ID NO:2 and the polypeptide sequence defined by SEQ ID NO:3 are enabled by Application 08/412,431 and have a priority date of March 29, 1995. As pointed out in the previous action and reiterated here, claims drawn to the specific sequences not included by SEQ ID NO:2 or 3 are not supported by other sequences are not enabled by the prior applications, and therefore have the April 16, 1996 priority date of Application 08/623,679. Applicant has failed to provide evidence that the *specific* other claimed sequences in the application are supported in either prior application 08/623,679 or 08/412,431. Therefore, the claims 31, 37, 40, 45, 51, 61-62, 65 and 68 have the March 29, 1995, priority date, and claims 29, 30, 32-36, 38, 39, 41-44, 46-50, 52-60, 63-64, 66, 67 have the April 16, 1996, priority date.

Deposit

4. Claims 29, 34-36, 54-56 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials, for the reasons set forth in the previous Office Action.

a. The response set forth on page 10-11 of paper no 13 and the declaration of Anita Meiklejohn filed 1 Sept 1999 as paper no 16 has been considered carefully but is deemed not to be persuasive. The response asserts that the Amendment to the specification and the statements of the Declaration are sufficient to overcome the rejection. This argument is not persuasive because the Tfohy030 and Nfohy030 clones were deposited after the effective filing date.

b. As stated int the previous Office Action, if deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell lines described in the specification as filed are the same as those deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

New Matter

5. The rejection of Claims 29, 37-39, 43, and 45 -50 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention has been withdrawn in view of the amendment to the claims to remove the new matter "15 contiguous amino acids".

6. The following NEW GROUNDS of rejection have been necessitated by amendment.

7. Newly amended Claims 29-43, 45-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been amended to recite "comprising at least 542 contiguous amino acids". The response states that support forth this amendment can be found on page 120, line 3. This argument is not persuasive because the text on page 120, line 3 recites, in closed language a " protein product of 542 amino acids in length". The language in the specification is narrower than that added to the claims. The specification does not provide support for the open language comprising at least contiguous 542 amino acids. Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

8. Newly amended Claims 51-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been amended to recite "comprises at least 74 nucleotides". The response states that support for this amendment can be found on page 120, line 10. This argument is not persuasive because the text on page 120, line 10 recites the negative limitation of "is missing 74 nucleotides beginning after 2926 in SEQ ID NO: 8". The language in the specification is narrower than that added to the claims. The specification does not provide support for the positive limitation of comprising at least 74 nucleotides. Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

9. Newly added Claims 57-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been amended to recite "has the sequence of a naturally-occurring mRNA present in a human melanocyte". The response states that support for this amendment can be found on page 113, line 28 to page 119, line 25, page 43, lines 8-18 and page 44, line 12 to page 45, line 23. This argument is not persuasive because the text on these pages does not appear to provide support for the phrase recite "has the sequence of a naturally-occurring mRNA present in a human melanocyte". Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

10. Newly added Claims 63-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims have been amended to recite "at least 94.4% identical" and "at least 86% identical" in reference to any molecules which have the particular amino acid or nucleotide acid sequence identities, respectively. The response states that support for this amendment can be found on page 119, lines 21-29. This argument is not persuasive because the text on page 119 recites the specific teaching that the mouse and human fohy030 sequences demonstrate a high degree of sequence similarity (86% identical at the nucleotide level and 94.4% identical at the amino acid level)". The language in the specification is narrower than that added to the claims, which recite any molecule which is at least those levels identical to any of the various sequences recites in the claims. The specific teaching of the specification does not provide support for the generic limitation as added. Additionally, the specification recites the percent identity in closed language while the claims recite a range of

identities with the qualifying phrase "at least". Applicant is required to either point to where the specification provides support for the phrase or to remove it from the claims.

11. The following NEW GROUNDS of rejection have been necessitated by amendment.

12. Claims 57-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The claims 57-62 are drawn to a polypeptide encoded by a sequence which "has the sequence of a naturally-occurring mRNA present in a human melanocyte". The criteria for sequences that constitute a naturally occurring allelic variant, however, are indefinite. The metes and bounds for what comprises a naturally occurring mRNA are undefined, particularly in the absence of any definition of which mutations would change the specific biochemical activity, as opposed to the tertiary structure, of the gene product.

b. Claims 57-62 are also indefinite for reciting "has the sequence" because it is not clear whether the protein, the first nucleotide acid molecule or the second nucleic acid molecule recited in the claims has the sequence of a naturally occurring mRNA present in a human or mouse melanocyte. Correcting the apparent lack of antecedent basis in the claims would be sufficient to obviate this rejection.

13. The specification is objected to under 35 U.S.C. 112, first paragraph, and Claims 57-62 are rejected under 35 U.S.C. 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to make polypeptides encoded by naturally occurring mRNA present in a human or mouse melanocyte.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims since the specification gives no guidance on or exemplification of how to make all of these types of modified proteins. The claims, as broadly written, read on amino acid sequences

comprising naturally occurring allelic variants. However, applicant has not enabled all of these types of alleles because it has not been shown where the differences in the disclosed sequences would be altered, or that these would result in a naturally occurring allele as opposed to a misfolded protein, truncated protein, etc.

The specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed protein can be tolerated that will allow the protein to retain functional properties. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (see Bowie et al cited in a previous Office Action). The specification and claims leave one skilled in the art to embark on experimentation of his own since no single allele has been disclosed or taught in the specification. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make every allele that will be correctly folded and functional as claimed. Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

14. Claims 57-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth proteins encoded by SEQ ID NO:2, 6, or 8 and therefore the written description is not commensurate in scope with the claims drawn to naturally occurring mRNA present in a human or mouse melanocyte.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Reiger et al cited in the previous Office Action clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome, and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structures of naturally occurring mRNA sequences are not defined. With the exception of SEQ ID NOS:2, 6, and 8, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides encoded by the various polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, in *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description... 'requires a precise

definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore only isolated polypeptides encoded by nucleotide sequence of amino acid sequences defined by SEQ ID NO:2, 6 or 8, but not "naturally occurring mRNAs" of the polypeptides, meet the written description provision of 35 U.S.C. 112, first paragraph.

15. Claims 63-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide consisting of SEQ ID NO: 3, 7 or 9 and polynucleotides encoding a polypeptide consisting of SEQ ID NO: 2, 6 or 8, does not reasonably provide enablement for polynucleotides encoding polypeptides that have at least 86 % identity with SEQ ID NO: 2, 6 or 8 or polypeptides that are at least 94.4% identical to SEQ ID NO: 3, 7 or 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. Sequence identity between two sequences has no common meaning within the art. See George et al; "Current Methods in Sequence Comparison and Analysis", in Macromolecular Sequencing and Synthesis, Selected Methods and Applications, pages 127-149 1988, Alan R. Liss, Inc and Barton et al "Protein Sequence Alignment and Database Scanning" in Protein Structure Prediction, A Practical Approach, 1996 IRL Press at Oxford University Press, Oxford, UK, pages 31-63). Barton et al teach that the "results of the analysis are entirely dependent on

the choice of scoring results" (page 130, col 1-2, bridging paragraph). George et al teach that percent sequence identity is not an objective property of molecules but is a value arrived at by using algorithms (page 130, columns 1-2, bridging paragraph). The scoring of gaps when comparing one nucleic acid sequence to another introduces uncertainty as to the percent of similarity between two sequences and applies equally to comparison of amino acid sequences.

c. The specification lacks specific algorithm and parameters used to determine percent identity, therefore, the specification provide insufficient guidance for one skilled in the art to determine the percent sequence identity of two sequences, albeit amino acid or nucleic acid sequences, without undue experimentation. A table or figure exemplifying a sequence alignment and numerical % sequence identity, without more elaboration, does not satisfy the need for explicit instructions in how to interpret the claims, because it is not possible to work backwards from the example to derive the algorithm and parameters used without undue experimentation.

d. In summary, the specification has not enabled determining which sequences are 94.4 or 86% identical in view of the lack of guidance concerning algorithms and parameters, as evidenced by Barton et al and George et al. The specification has provided insufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including an enormous number of variants of the gene encoding SEQ ID NO 3, 7 or 9. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polynucleotides encoding polypeptides consisting of SEQ ID NO: 2, 6, and 8 is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claim Rejections - 35 USC § 103

16. Newly amended Claims 51 and 54-56 and newly added claims 61-62 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No 5,487,985 ('985) in view of Zubay

(Biochemistry, page 912, Adison-Wesley Publishing Company Inc. 1984), for the reasons set forth in the previous Office Action

a. The response set forth on page 11-12 has been considered carefully but is deemed not to be persuasive. The response argues that the amendment tot he claims to recite comprising 74 nucleotides would be sufficient to obviate this rejection. This argument is not persuasive because the claims retain the low stringency conditions of 42oC, 0.2X SSC and 0.1%SDS and because the claims are drawn to polypeptides encoded by at least 74 bases of nucleic acid sequences that hybridize under at 42 degrees Celsius in 0.2XSSC, 0.1% SDS to SEQ ID NO:2, or the cDNA clones contained in NRRL Deposit No. B-21426, ATCC Accession No. 97880, or ATTC Accession No. 97881.

b. '985 teaches a 26 base long sequence (SEQ ID NO:10) that would hybridize to the claimed sequences at the specified low stringency conditions. Given their broadest possible scope, the claims are drawn to cases in which even a small amount of the sequence would hybridize. SEQ ID NO: 10 of '985 would hybridize to the claimed sequence in smaller amounts under the claimed hybridization conditions, but nevertheless would hybridize, as set froth in the previous office action.

c. Amending the claims to recite the more stringent hybridization conditions of 68oC, 0.1X SSC, 0.1% SDS would obviate this rejection.

17. Newly amended Claims 52-56 and newly added claims 61-62 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No 5,565,340 ('340) in view of Zubay (Biochemistry, page 912, Adison-Wesley Publishing Company Inc. 1984), for the reasons set forth in the previous Office Action

a. The response set forth on page 11-12 has been considered carefully but is deemed not to be persuasive. The response argues that the amendment tot he claims to recite comprising 74 ~~nucelotides~~ nucleotides would be sufficient ~~or~~ to obviate this rejection. This argument is not persuasive JB

because the claims have been amended to recite polypeptides encoded by at least 74 bases of nucleic acid sequences that hybridize under at 42 degrees Celcius in 0.2XSSC, 0.1% SDS to SEQ ID NOS:6 or 8, or the cDNA clones contained in NRRL Deposit No. B-21426, ATTC Accession No. 97880, or ATTC Accession No. 97881.

b. As set forth in the previous Office Action, '340 teaches a 44 base long sequence (SEQ ID NO:5) that would hybridize to the claimed sequences at the specified conditions. Given their broadest possible scope, the claims are drawn to cases in which even a small amount of the sequence would hybridize. SEQ ID NO: 5 of '340 would hybridize to the claimed sequence in smaller amounts under the claimed hybridization conditions, but nevertheless would hybridize.

c. Amending the claims to recite the more stringent hybridization conditions of 68oC, 0.1X SSC, 0.1% SDS would obviate this rejection.

Specification

18. The disclosure is objected to because of the following informalities: the first line of the specification states that this application is a divisional of copending application 08/632,679, however, it appears that this sentence contains a typographical error in the application number. Additionally the status of all applications needs to be updated to show that they have gone on to abandoment or issue.

Appropriate correction is required.

Oath/Declaration

19. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

it recites that this application is a divisional of copending application 08/623,679, however this application number differs from that on the first line of the specification. Amending the first line of the specification to correct the pparent typographical error, or filing a new declaration reciting the same application number as found in the first line of the specification would be sufficient to obviate this objection.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie E. Burke, née Reeves, Ph.D, whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

23. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

JEBurke

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JULIE BURKE
PRIMARY EXAMINER